Sexually Transmitted Disease Surveillance 1998 Supplement

Division of STD Prevention
November 1999

Gonococcal Isolate Surveillance Project (GISP)
Annual Report - 1998

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for HIV, STD, and TB Prevention
Division of STD Prevention
Atlanta, Georgia 30333

Centers for Disease Control and Prevention . . . . . Jeffrey P. Koplan, M.D., M.P.H.
Director

National Center for
HIV, STD, and TB Prevention . . . . . Helene D. Gayle, M.D., M.P.H.
Director

Division of STD Prevention . . . . . Judith N. Wasserheit, M.D., M.P.H.
Director

Epidemiology and
Surveillance Branch . . . . . Michael E. St. Louis, M.D.
Chief

Surveillance and Special
Studies Section . . . . . William C. Levine, M.D., M.Sc.
Chief

Gonococcal Isolate
Surveillance Project . . . . . Susan A. Wang, M.D., M.P.H.
Coordinator

Statistics and Data
Management Branch . . . . . Russell H. Roegner, Ph.D.
Chief

Melinda Flock, M.S.P.H.
Deputy Chief

National Center for
Infectious Diseases . . . . . James M. Hughes, M.D.
Director

Division of AIDS, STD, and
TB Laboratory Research . . . . . Harold W. Jaffe, M.D.
Director

Bacterial STD Branch . . . . . Joan S. Knapp, Ph.D.
Chief

Copyright Information

Suggested Citation

Division of STD Prevention. Sexually Transmitted Disease Surveillance 1998 Supplement: Gonococcal Isolate Surveillance Project (GISP) Annual Report - 1998. Department of Health and Human Services, Public Health Service. Atlanta: Centers for Disease Control and Prevention, November 1999.

Copies can be obtained from the Epidemiology and Surveillance Branch, Division of STD Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, NE, Mailstop E-02, Atlanta, Georgia 30333.

This report is available from the Internet via the CDC home page address
http://www.cdc.gov/ncidod/dastlr/gcdir/Resist/gisp.html
The 1998 STD Surveillance Report may be found at
http://www.cdc.gov/nchstp/dstd/Stats_Trends/1998_Surv_Rpt_main_pg.htm.

Acknowledgments

Publication of this report would not have been possible without the substantial contributions of the sexually transmitted disease clinics which participated in the Gonococcal Isolate Surveillance Project, and the laboratories which performed all the susceptibility testing. We appreciate the contributions of the regional laboratory directors: Carlos del Rio (Emory University, Atlanta, GA), King K. Holmes (University of Washington, Seattle, WA), Edward W. Hook (University of Alabama, Birmingham, AL), Franklyn N. Judson (Denver Health and Hospitals, Denver, CO), Gary W. Procop (The Cleveland Clinic Foundation, Cleveland, OH), and W. L. Whittington (University of Washington, Seattle, WA).

This report was prepared by the following staff members of the Division of STD Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention: Susan A. Wang, Alesia Jester Harvey, and William C. Levine; and the following staff members of the Division of AIDS, STD, and TB Laboratory Research, National Center for Infectious Diseases, Centers for Disease Control and Prevention: Joan S. Knapp, David L. Trees, Manhar Parekh, and Sandra W. Neal.

GONOCOCCAL ISOLATE SURVEILLANCE PROJECT (GISP)
ANNUAL REPORT - 1998

Introduction

Gonorrhea is the second most frequently reported communicable disease in the United States. Overall gonorrhea rates in the United States declined 72% since 1975. However, between 1997 and 1998, the rate increased by 8.9% from 122.0 cases per 100,000 persons to 132.9 (**Figure 1**). Gonorrhea rates remain high in the southeastern states, among minorities, and among adolescents of all racial and ethnic groups (**Figures 2, 3, and 4**).[1] The health impact of gonorrhea is largely related to its role as a major cause of pelvic inflammatory disease, which frequently leads to infertility or ectopic pregnancy.[2] In addition, recent data suggest that gonorrhea facilitates HIV transmission.[3,4]

Control of gonorrhea has been complicated by the development of resistance to antimicrobial agents. The appearance of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) and chromosomally mediated penicillin- and tetracycline-resistant *N. gonorrhoeae* (CMRNG) in the 1970s eventually led to the abandonment of these drugs as therapies for gonorrhea. The currently recommended primary therapies for gonorrhea are two broad-spectrum cephalosporins, ceftriaxone and cefixime, and two fluoroquinolones, ciprofloxacin and ofloxacin.[5] However, fluoroquinolone-resistant *N. gonorrhoeae* have been reported from many parts of the world, including the United States.[6-9]

GISP Overview

The Gonococcal Isolate Surveillance Project (GISP) was established in 1986 to monitor trends in antimicrobial susceptibilities of strains of *N. gonorrhoeae* in the United States in order to establish a rational basis for the selection of gonococcal therapies.[10] GISP is a collaborative project between selected sexually transmitted diseases (STD) clinics, five regional laboratories, and the Centers for Disease Control and Prevention (CDC) (Division of STD Prevention, National Center for HIV, STD, and TB Prevention, and the Division of AIDS, STD, and TB Laboratory Research, National Center for Infectious Diseases).

In GISP, *N. gonorrhoeae* isolates are collected from the first 20 men with urethral gonorrhea attending sexually transmitted diseases clinics each month in 28 cities in the United States. At regional laboratories, the susceptibilities of these isolates to antimicrobial agents, including broad-spectrum cephalosporins and fluoroquinolones currently recommended for the treatment of uncomplicated gonorrhea, are determined. Minimum inhibitory concentrations (MICs) are measured, and resistance interpreted according to criteria recommended by the National Committee for Clinical Laboratory Standards (NCCLS).[11,12]

Important GISP findings have included the ongoing high prevalence of resistance to penicillin and

tetracycline; the appearance, at low levels, of decreased susceptibility and resistance to the fluoroquinolones; the absence of resistance to the broad-spectrum cephalosporins; and the increasing proportion of gonorrhea cases coming from men who have sex with men.[7-9,13] These findings contributed to the development of CDC's STD treatment recommendations in 1993 and 1998,[5,14] and stimulated further investigation of the increase in gonorrhea among men who have sex with men.[13]

1998 GISP Sites

A total of 28 STD clinics contributed 4,712 gonococcal isolates to GISP in 1998 (**Figure 5**). Eighteen sites have participated continuously since 1988: Albuquerque, Anchorage, Atlanta, Baltimore, Birmingham, Cincinnati, Denver, Honolulu, Long Beach, New Orleans, Philadelphia, Phoenix, Portland, San Antonio, San Diego, San Francisco, Seattle, and West Palm Beach. Eight sites joined GISP after 1988: Fort Lewis in 1989; Cleveland, Kansas City, Nassau County, and Orange County in 1991; Minneapolis in 1992; Chicago in 1996; and Miami in 1998. Two sites have had intermittent participation: Fort Bragg 1987-90 and 1997-98, and St. Louis 1987-93 and 1995-8. The GISP Regional Laboratories are located in Atlanta, Birmingham, Cleveland, Denver, and Seattle.

DESCRIPTION OF GISP DATA

Aggregate data from all GISP sites are described and illustrated in the first part of this report. The clinic-specific data illustrate substantial geographic variation in patient characteristics and antimicrobial susceptibility of gonococcal strains; clinic-specific figures are provided in the second part of this report.

Demographic and Clinical Characteristics

Age The age distributions of GISP participants in 1988 and 1998 are shown in **Figure 6**. Ages ranged from 13 to 82 years in 1998. The age distribution has previously been shown to be similar to the age distribution of nationally reported cases of gonorrhea in men.[15]

Race/Ethnicity The 1998 race/ethnicity distribution of GISP participants is shown in **Figure 7**. Previous comparison has shown that GISP participants include proportionally more Hispanics than nationally reported gonorrhea in men;[15] several GISP sites where Hispanics account for a high proportion of gonorrhea cases explain this difference.

Sexual Orientation In 1998, 12.0% of GISP participants were men who have sex with men (MSM), compared with 4.0% in 1988 (**Figure 8**). Nine clinics reported the majority (439/503; 87.3%) of MSM in GISP in 1998; in all nine clinics, the proportion of participants who were MSM increased in 1997, 1998, or both. The percentages of isolates that came from MSM in these nine clinics from 1988 through 1998 are shown in **Figure 9**. A study of eight of these cities performed in 1996 showed that in five of the eight (Honolulu, Portland, San Diego, San

Francisco, and Seattle) the proportional increases corresponded to absolute increases in numbers of MSM with gonorrhea.[13]

Reason for Clinic Attendance Most GISP participants in 1998 presented to the clinic as volunteers; others were gonorrhea contacts or presented for test-of-cure cultures (**Figure 10**). There has been little change in this distribution over time. Dysuria and/or urethral discharge was present in 96.7% of GISP participants in 1998; 3.3% had no symptoms.

History of Gonorrhea The percentage of GISP participants who reported a history of gonorrhea (ever) increased from 38.3% in 1991, the first year this information was collected, to a peak of 49.9% in 1996, but declined to 46.8% in 1998. The percentage of GISP participants with a documented previous episode of gonorrhea in the last 12 months decreased from 21.5% in 1992, the first year this information was collected, to 17.5% in 1998 (**Figure 11**).

Gonorrhea Treatment The treatments used for gonorrhea are shown in **Figure 12**. The proportion of GISP cases treated with cephalosporins decreased from a high of 84.6% in 1990 to 65.4% in 1998, while the proportion treated with fluoroquinolones (ciprofloxacin or ofloxacin) increased from none in 1988 to 31.2% in 1998.

Susceptibility to Antimicrobial Agents

Antimicrobial Resistance Criteria

Antimicrobial resistance in *N. gonorrhoeae* is defined by the criteria recommended by the NCCLS:[12]

Penicillin, MIC ≥2.0 µg/ml
Tetracycline, MIC ≥2.0 µg/ml
Spectinomycin, MIC ≥128.0 µg/ml
Ciprofloxacin, MIC 0.125 - 0.5 µg/ml (intermediate resistance)
Ciprofloxacin, MIC ≥1.0 µg/ml (resistance)
Ceftriaxone, MIC ≥0.5 µg/ml (decreased susceptibility)
Cefixime, MIC ≥0.5 µg/ml (decreased susceptibility)

Criteria for resistance to ceftriaxone, cefixime, erythromycin, and azithromycin have not been established.

Susceptibility to Penicillin and Tetracycline

Overall, 29.4 % (1384/4712) of isolates collected in 1998 were resistant to penicillin, tetracycline, or both (**Figure 13**); this proportion has been relatively constant since 1988. The percentage of penicillinase-producing *N. gonorrhoeae* (PPNG) declined from a peak of 11.0% in 1991 to 3.0% in 1998 (**Figure 14**). In contrast, the percentage of isolates with chromosomally mediated resistance to penicillin (PenR) has increased annually, from 0.5% in 1988 to 5.1% in 1998 (**Figure 15**). The prevalence of plasmid-mediated resistance to tetracycline (TRNG), 6.6% in

1998, has varied little since 1988 (**Figure 14**). Similarly, the prevalence of chromosomally mediated resistance to tetracycline only (TetR), 6.8% in 1998, has been relatively stable since 1989, except for a transient increase in 1995 (**Figure 15**). However, the prevalence of isolates with chromosomally mediated resistance to both penicillin and tetracycline (CMRNG) increased from 3.0% in 1989 to 7.2% in 1998. The prevalence of isolates with plasmid-mediated resistance to both penicillin and tetracycline (PPNG-TRNG), 0.7% in 1998, continues to be low.

Susceptibility to Spectinomycin

All isolates were susceptible to spectinomycin in 1998. There have been five spectinomycin-resistant isolates in GISP; their locations and years were: St. Louis-1988, Honolulu-1989, San Francisco-1989, Long Beach-1990, and West Palm Beach-1994.

Susceptibility to Ceftriaxone

The distribution of MICs to ceftriaxone in 1988 and 1998 are shown in **Figure 16**. Over this period, there has been a subtle shift towards higher ceftriaxone MICs. In 1998, all isolates were susceptible to ceftriaxone.

Susceptibility to Cefixime

The distributions of MICs to cefixime in 1992 (the first year of cefixime susceptibility testing) and 1998 are shown in **Figure 17**. In 1998, five isolates had decreased susceptibility to cefixime: two isolates from St. Louis with MICs=0.5 µg/ml and three isolates from Philadelphia with MICs=1.0 µg/ml. One isolate from each location was also TetR.

Susceptibility to Ciprofloxacin

The distributions of MICs to ciprofloxacin in 1990 (the first year of ciprofloxacin susceptibility testing) and 1998 are shown in **Figure 18**. A total of 1.0% (48/4712) of isolates exhibited intermediate resistance or resistance to ciprofloxacin (MICs ≥0.125 µg/ml) compared with 0.6% (29/4544) of isolates tested in 1997 (**Figure 19**).

In 1998, 0.9% (44/4712) of all GISP isolates exhibited intermediate resistance to ciprofloxacin (MICs 0.125-0.5 µg/ml). Of these isolates, 29.5% (13/44) came from Cleveland patients, where they accounted for 5.8% (13/225) of Cleveland isolates and 25.0% (11/44) came from Atlanta patients, where they accounted for 4.8% (11/227) of Atlanta isolates tested in 1998. Isolates of *N. gonorrhoeae* exhibiting intermediate resistance to ciprofloxacin were also found in Anchorage, Baltimore, Cincinnati, Honolulu, New Orleans, St. Louis, San Antonio, San Francisco, Seattle, and West Palm Beach in 1998.

Four isolates (0.1%; 4/4712) were resistant to ciprofloxacin (MICs ≥1.0 µg/ml) in 1998; the locations, number, and MICs of these isolates were: Cincinnati (1), 1.0 µg/ml; Honolulu (2), 1.0 µg/ml and 2.0 µg/ml; and San Francisco (1), 8.0 µg/ml.

The clinical significance of strains with ciprofloxacin MICs of 0.125-0.5 µg/ml, when a fluoroquinolone is used to treat a gonococcal infection, is not well established. However, one study of infections with resistant strains treated with ciprofloxacin 500 mg orally showed a treatment failure rate of 45% for strains with MICs of ≥4.0 µg/ml.[16] Gonococcal isolates with intermediate resistance and resistance to ciprofloxacin also have intermediate resistance and resistance to other fluoroquinolones. Criteria recommended for interpreting ofloxacin MICs are: intermediate resistance, MICs 0.5-1.0 µg/ml; resistance, MICs ≥2.0 µg/ml.[12]

ADDITIONAL RESOURCES

Recent publications using GISP data include a paper in the Journal of Infectious Diseases[7] and MMWR articles in September, 1997[13] and March, 1998.[9] Presentations of GISP data were made at the Annual Meeting of the Infectious Diseases Society of America in September, 1997,[17] the International Congress of STDs in October, 1997,[18] and the International Conference on Emerging Infectious Diseases in March, 1998.[19] Detailed information on susceptibilities of *N. gonorrhoeae* isolates from each clinic may be obtained through CDC's website (http://www.cdc.gov/ncidod/dastlr/gcdir/Resist/gisp.html). Updates on emerging resistance of *N. gonorrhoeae* strains to the fluoroquinolones may also be obtained through CDC's website (http://www.cdc.gov/ncidod/dastlr/gcdir/gono.html). Additional surveillance data on *N. gonorrhoeae* and other sexually transmitted diseases may be found in the 1998 STD Surveillance Report (http://www.cdc.gov/nchstp/dstd/Stats_Trends/1998_Surv_Rpt_main_pg.htm).

REFERENCES

1. Fox KK, Whittington WL, Levine WC, Moran JS, Zaidi AA, Nakashima AK. Gonorrhea in the United States, 1981-1996: Demographic and geographic trends. *Sex Transm Dis* 1998; 386- 93.

2. McCormack WM. Pelvic inflammatory disease. *N Engl J Med*. 1994;330:115-119.

3. Laga M, Manoka A, Kivuvu M, et al. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. *AIDS*. 1993;7:93-102.

4. Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet* 1997;349:1868-73.

5. CDC. 1998 Guidelines for treatment of sexually transmitted diseases. *MMWR* 1998;47(no.

RR-1).

6. Knapp JS, Fox KK, Trees DL, Whittington WL. Fluoroquinolone resistance in *Neisseria gonorrhoeae*. *Emerg Infect Dis* 1997; 3:33-39.

7. Fox KK, Knapp JS, Holmes KK, Hook EW, Judson FN, Thompson SE, Washington JA, and Whittington WL. Antimicrobial resistance in *Neisseria gonorrhoeae* in the United States 1988- 1994: the emergence of resistance to the fluoroquinolones. *J Infect Dis* 1997;175:1396-1403.

8. CDC. Fluoroquinolone resistance in *Neisseria gonorrhoeae* - Colorado and Washington, 1995. *MMWR* 1995;44:761-4.

9. CDC. Fluoroquinolone-resistant *Neisseria gonorrhoeae*--San Diego, California, 1997. *MMWR* 1998;47:405-408.

10. Schwarcz SK, Zenilman JM, Schnell D, et al. National surveillance of antimicrobial resistance in *Neisseria gonorrhoeae. JAMA* 1990; 264:1413-1417.

11. National Committee for Clinical Laboratory Standards. Approved standard M7 - A3. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Villanova, Pa. 1993.

12. National Committee for Clinical Laboratory Standards. Approved standard M100-38. Performance standards for antimicrobial susceptibility testing. Wayne, PA: National Committee for Clinical Laboratory Standards, 1998.

13. CDC. Gonorrhea among men who have sex with men--selected sexually transmitted diseases clinics, 1993-1996. *MMWR* 1997;46:889-892.

14. CDC. 1993 Sexually transmitted diseases treatment guidelines. *MMWR* 1993;42(no. RR-14).

15. Division of STD Prevention. Gonococcal Isolate Surveillance Project (GISP): Annual Report--1996. U.S. Department of Health and Human Services, Public Health Service. Atlanta: Centers for Disease Control and Prevention, 1997.

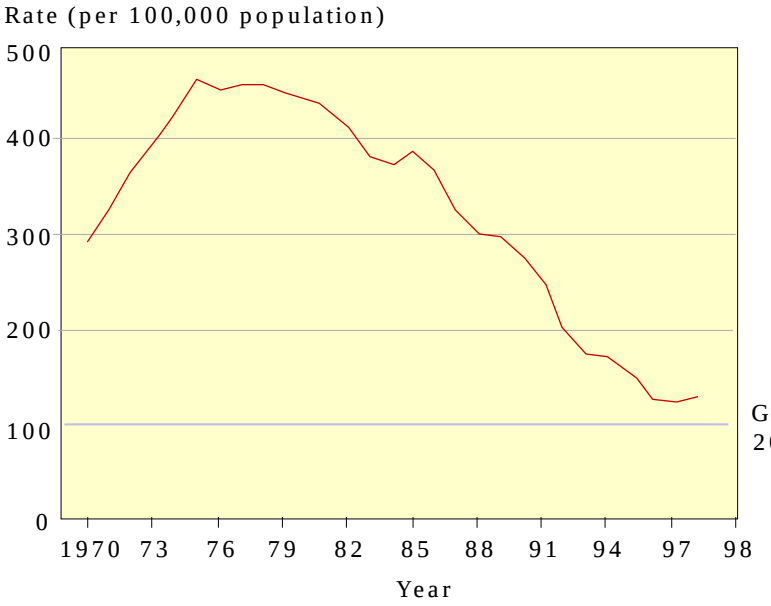
16. Aplasca MR, Pato-Mesola V, Klausner J, Tuazon C, Whittington WL, Holmes KK. High rates of failure after treatment with ciprofloxacin--are fluoroquinolones no longer useful for gonorrhea treatment? Fourth International Congress on AIDS in Asia and the Pacific; Manila, Philippines, October 25-29, 1997.

17. Fox KK, Levine WC, and Knapp JS. Changing epidemiology of gonorrhea: findings from a sentinel system [abstract]. Infectious Diseases Society of America, San Francisco, September 13-16, 1997.

18. Fox KK and Knapp JS. Sentinel surveillance for antimicrobial resistance in *Neisseria gonorrhoeae* [abstract #150]. International Congress of Sexually Transmitted Diseases, Seville, Spain, October 19-22, 1997.

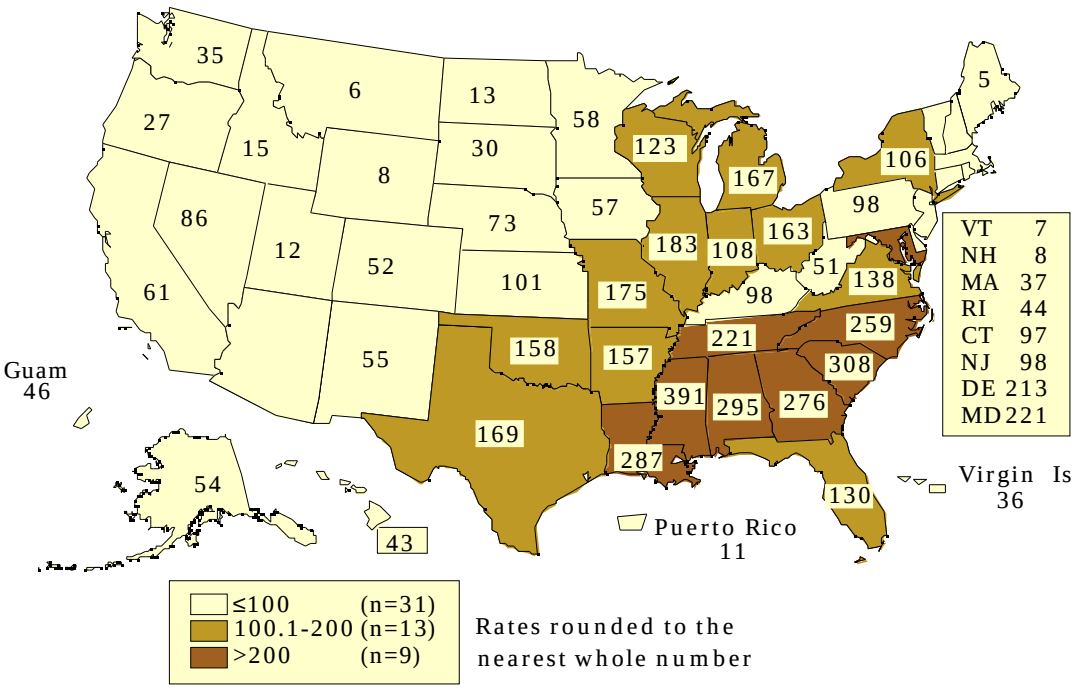
19. Fox KK, Levine WC, and Knapp JS. Fluoroquinolone-resistant *Neisseria gonorrhoeae* in the United States, 1990-1996 [abstract #9835]. International Conference on Emerging Infectious Diseases, Atlanta, Georgia, March 8-11, 1998.

Figure 1. Gonorrhea -- Reported rates: United States, 1970-1998 and the Healthy People year 2000 objective



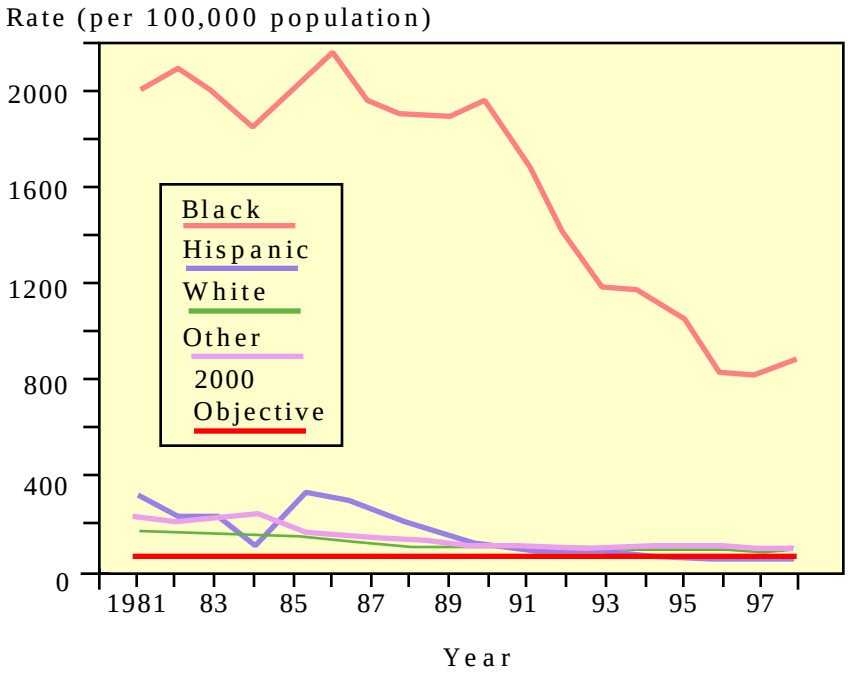
Note: Georgia did not report gonorrhea statistics in 1994.

Figure 2. Gonorrhea -- Rates by state: United States and outlying areas



Note: The total rate for gonorrhea for the United Sttates and outlying areas (including Guam, Puerto Rico and Virgin Islands) was 131.1 per 100,000 population. The Healthy People year 2000 objective is 100 per 100,000 population

Figure 3. Gonorrhea -- Rates by race and ethnicity: United States, 1981-1998 and the Healthy People yearr 2000 objective



Note: Georgia did not report gonorrhea statistics in 1994.

Figure 4. Gonorrhea -- Age- and gender-specific rates: United States, 1998

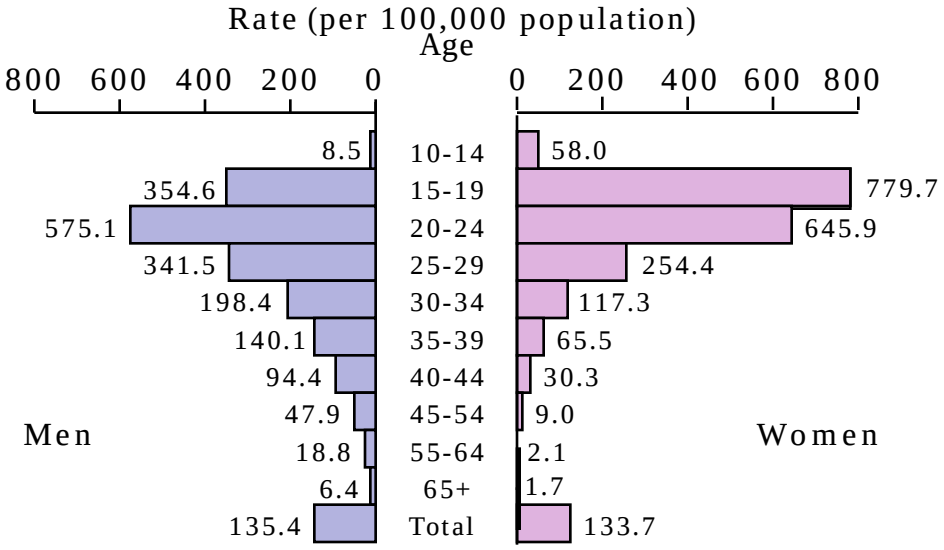
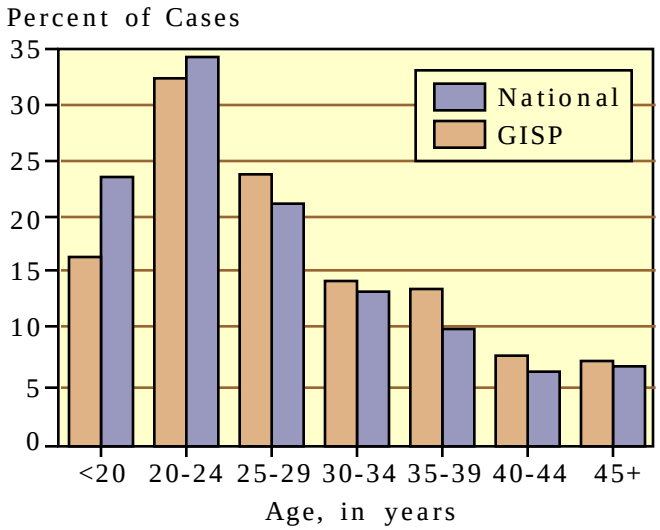


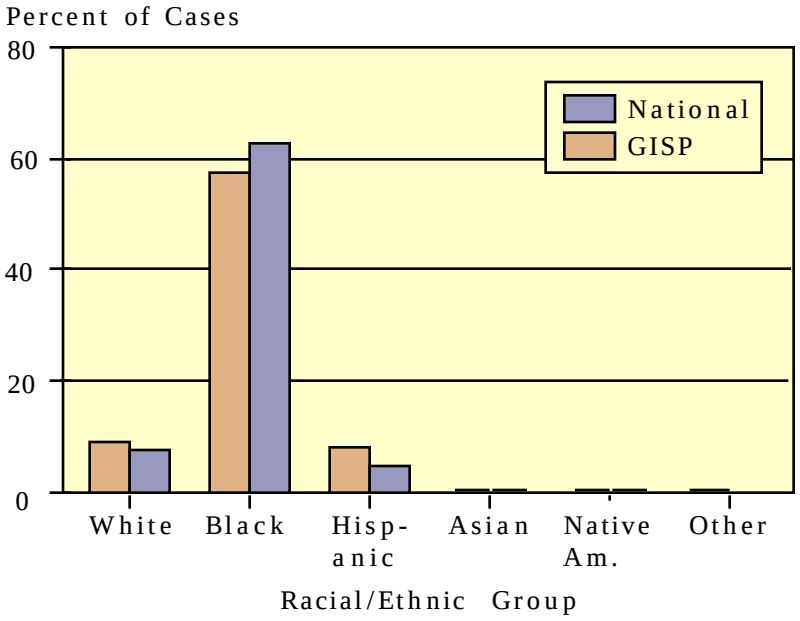
Figure 5. Gonococcal Isolate Surveillance Project (GISP) -- Location of participating clinics and regional laboratories: United States, 1998

Figure 6. Age distribution of GISP participants and nationally reported gonorrhea cases in men, 1998



Note: The age <20 category includes ages 10-19 for national cases, and ages 13-19 for GISP; over 99% of the GISP cases in the <20 category are ages 15-19. National cases with unknown ages were excluded.

Figure 7. Race distribution of GISP participants and nationally reported cases of gonorrhea in men, 1998



Note: The "Other" category is not used in natioanl gonorrhea reporting. National cases with unknown race were excluded.

Figure 8. Percentage of GISP cases that were men who have sex with men (MSM)

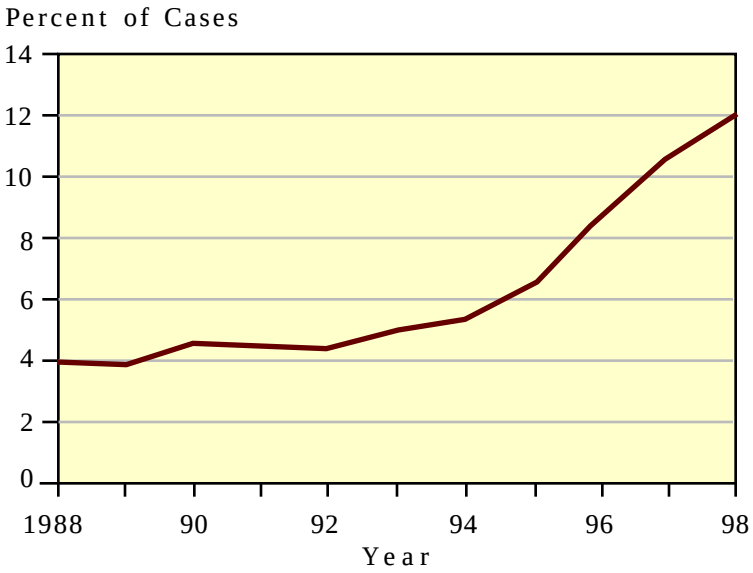
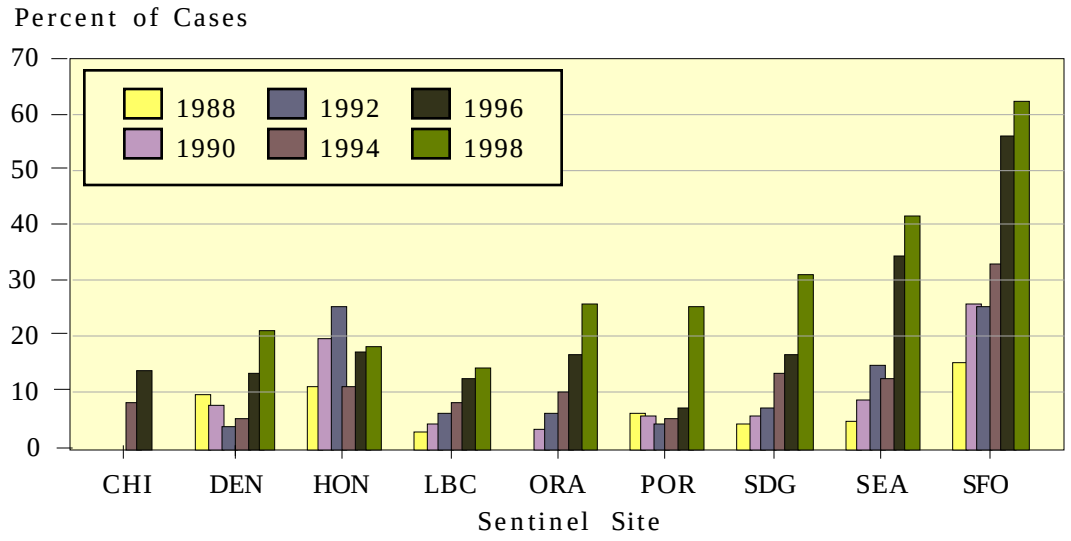
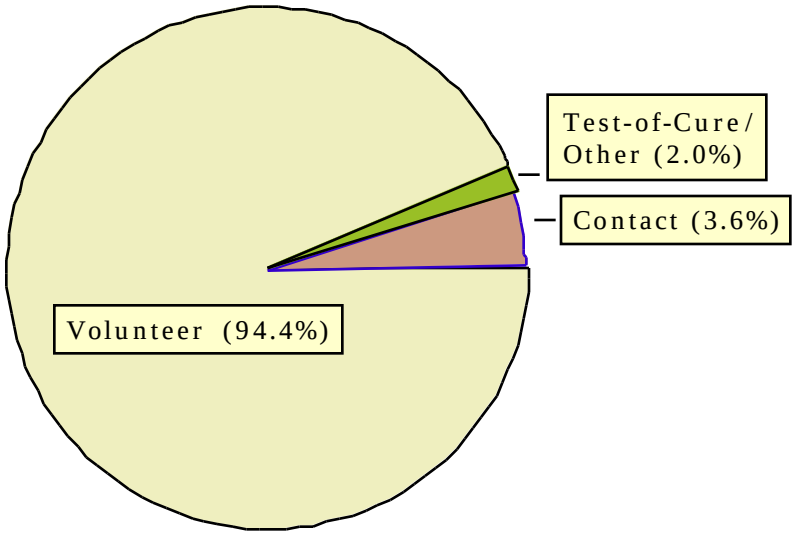


Figure 9. Percentage of GISP isolates from men who have sex with men in nine clinics, 1988-1989



CHI=Chicago, IL
(first year 1996 for this site)
DEN=Denver,CO
HON=Honolulu, HI
LBC=Long Beach, CA
ORA=Orange Co, CA
(first year 1991 for this site)
POR=Portland
SDG=San Diego, CA
SEA=Seattle, WA
SFO=San Francisco

Figure 10. Reason for clinic attendance among GISP participants, 1998



Contact=has sexual partner with gonorrhea

Figure 11. History of gonorrhea in GISP participants

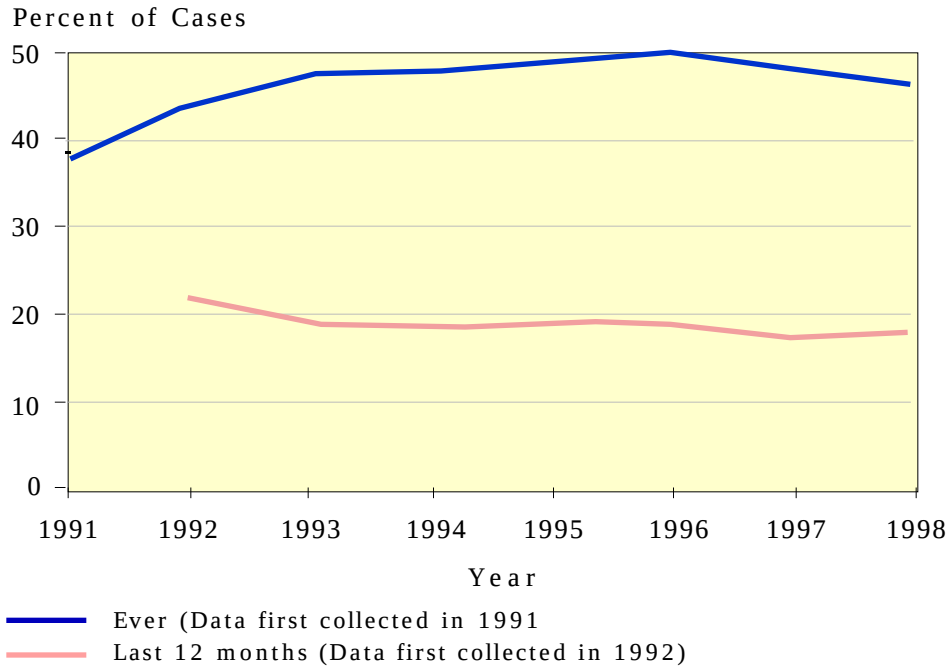


Figure 12. Drugs used to treat gonorrhea in GISP participants

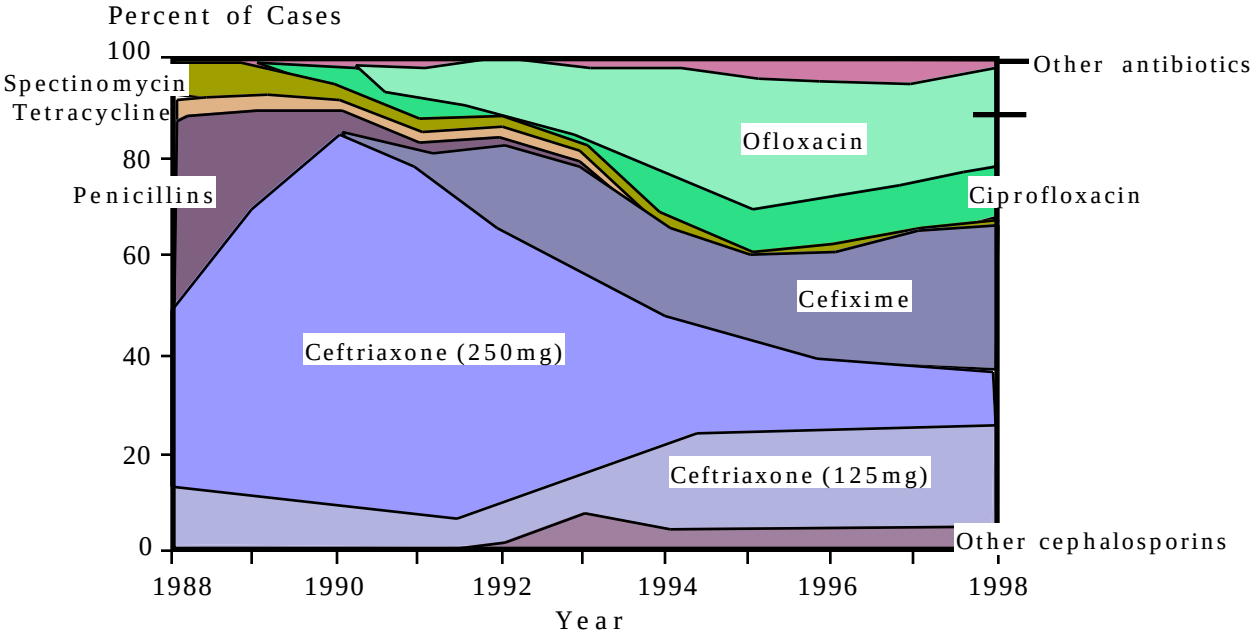
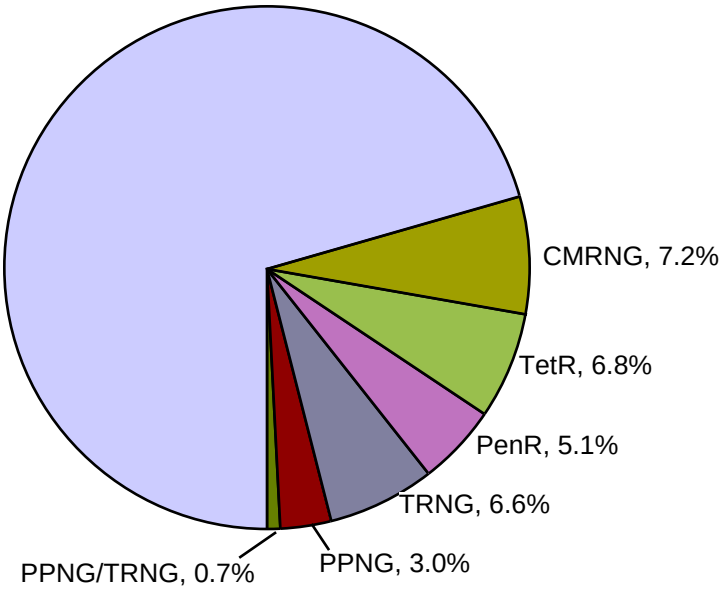


Figure 13. Penicillin and tetracycline resistance among GISP isolates, 199



PPNG = penicillinase-producing *N. gonorrhoeae*

TRNG = plasmid-mediated tetracycline resistant *N. gonorrhoeae*

PPNG-TRNG = plasmid-mediated penicillin and tetracycline resistant *N. gonorrhoeae*

PenR = chromosomally mediated penicillin-resistant *N. gonorrhoeae*

TetR = chromosomally mediated tetracycline-resistant *N. gonorrhoeae*

CMRNG = chromosomally mediated penicillin and tetracycline resistant *N. gonorrhoeae*

Figure 14. Plasmid-mediated resistance to penicillin and tetracycline among GISP isolates

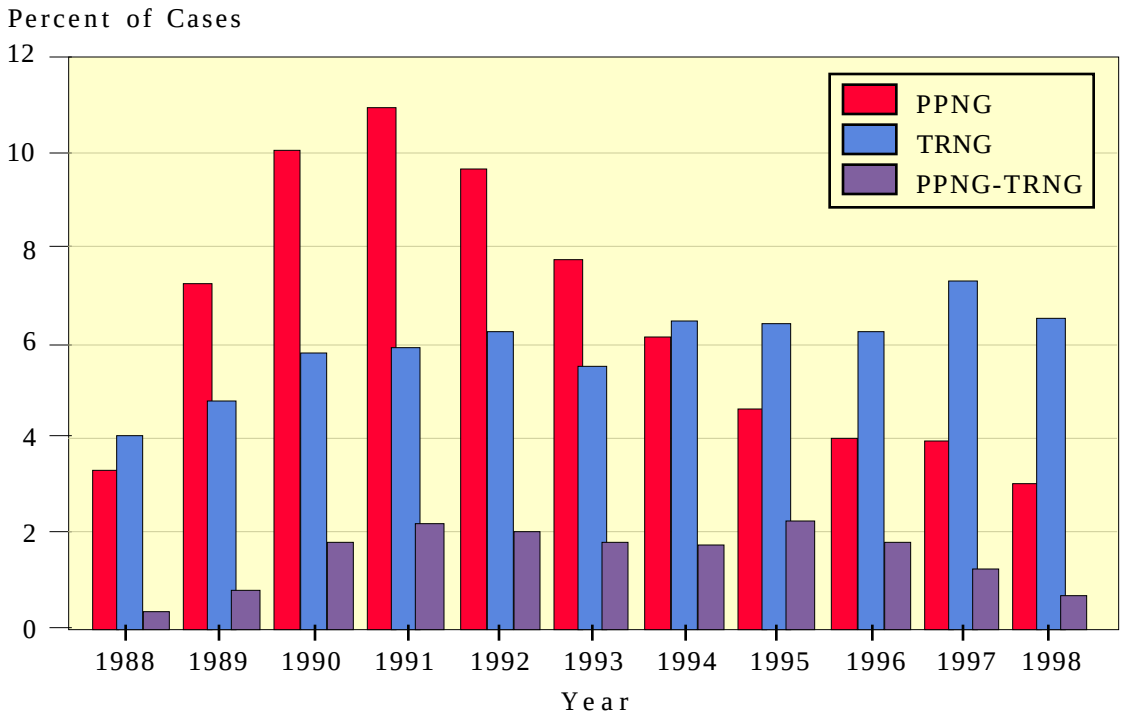


Figure 15. Chromosomally mediated resistance to penicillin and tetracycline among GISP isolates

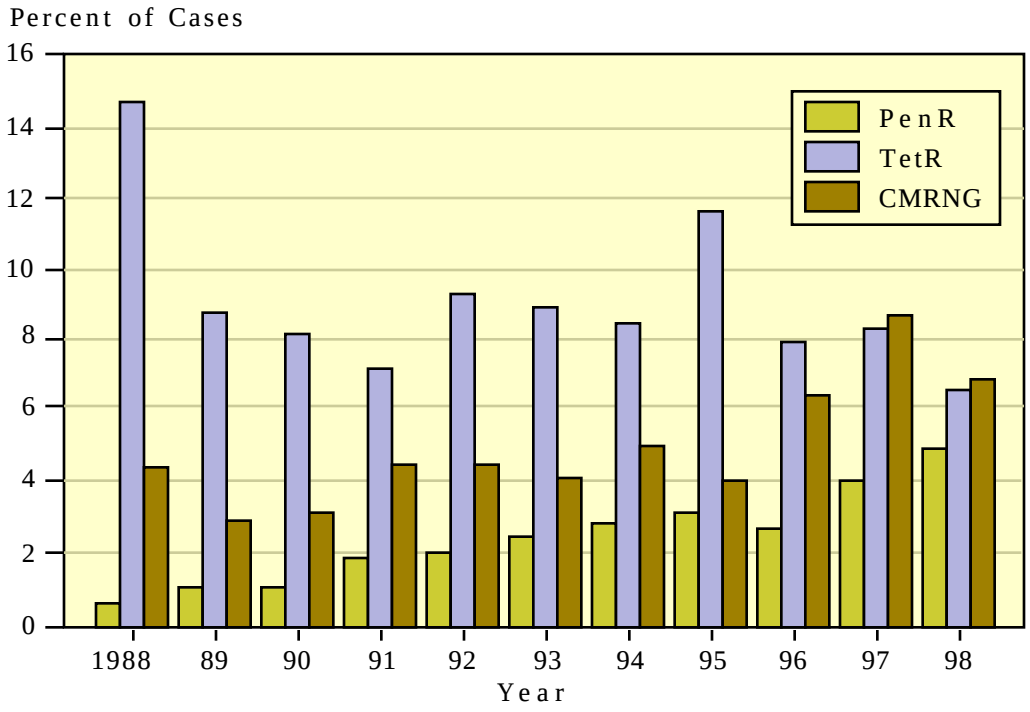


Figure 16. Distribution of MICs to ceftriaxone among GISP isolates, 1988 and 1998

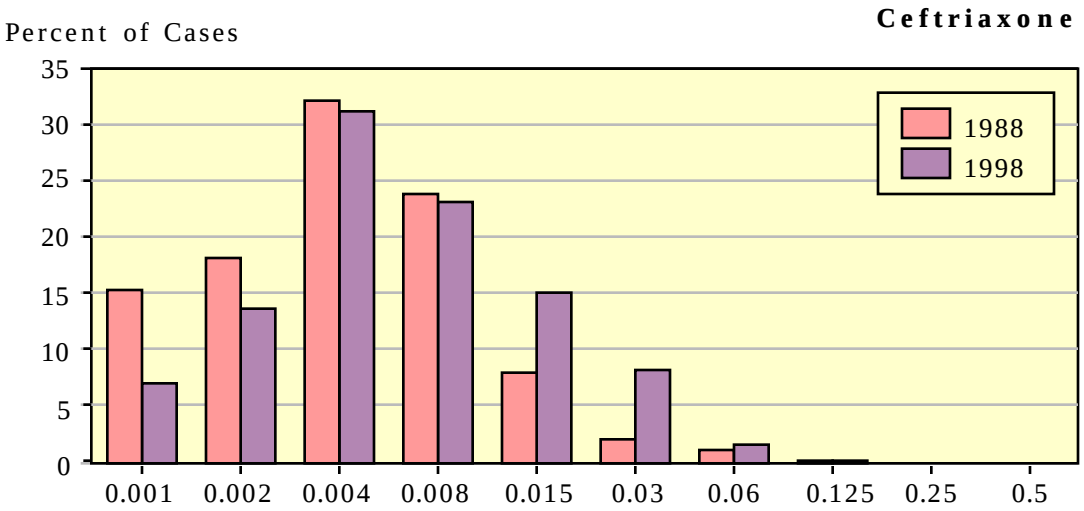


Figure 17. Distribution of MICs to cefixime among GISP isolates, 1992 and 1998

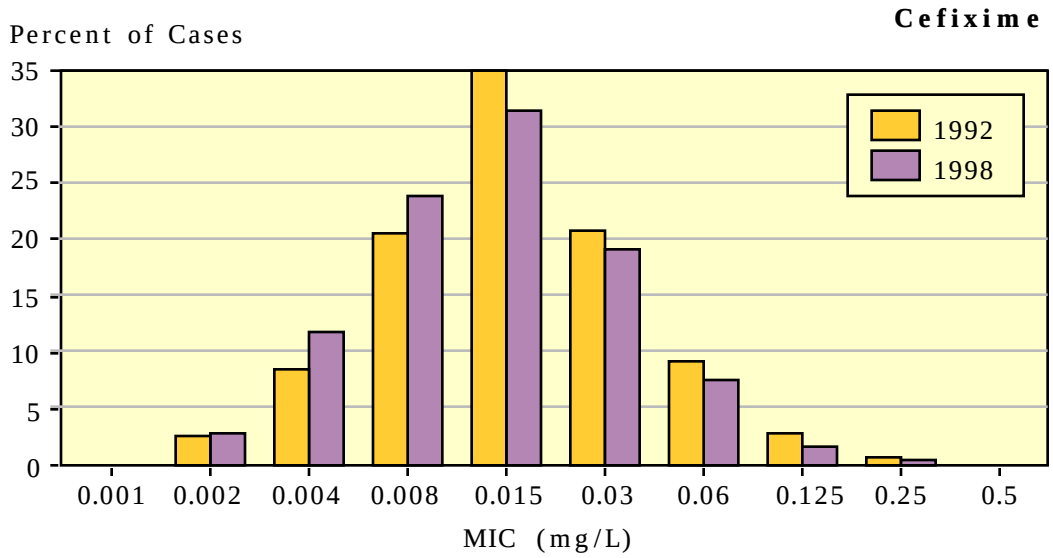


Figure 18. Distribution of MICs to ciprofloxacin among GISP isolates, 1990 and 1998

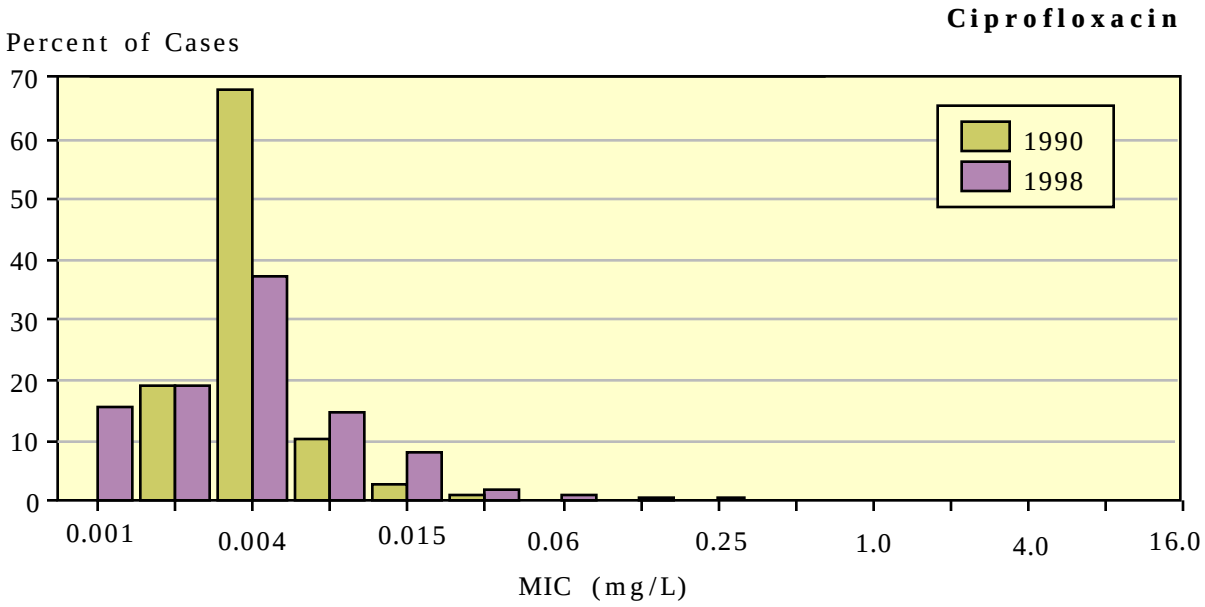


Figure 19. Percentage of GISP isolates with intermediate resistance or resistance to ciprofloxacin